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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Olivier Neckebrock, et al.

Confirmation No.: **8401**

Application No.: **10/539,918**

Group Art Unit: **Not yet Assigned**

Filing Date: **February 17, 2006**

Examiner: **Not Yet Assigned**

For: **Process For the Preparation of and Crystalline Forms of Optical Enantiomers of Modafinil**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JOHN P. MALLAMO, PH.D.

I, John P. Mallamo, Ph.D. hereby declare the following:

(1) I received a Bachelor of Science in Chemistry from Colorado State University in 1977, and a Ph.D. in Organic Chemistry from Johns Hopkins University in 1981. From January 2002 to the present, I have served as Vice President, World Wide Chemical Research & Development, at Cephalon, Inc. 41 Moores Road, P.O. Box 4011, Frazer, PA 19355. A copy of my current *curriculum vitae* is attached hereto as Exhibit 1.

(2) Modafinil is the active ingredient in a commercial pharmaceutical product made by Cephalon Inc. It exists in (-) and (+) isomeric forms and as a racemic mixture.

(3) I have reviewed and am familiar with the above-captioned patent application which, among other things, describes polymorphic forms of (-)-modafinil and methods of preparing same. In particular, the patent application describes a particular polymorph of (-)-modafinil that is denominated as "Form I." This polymorph is described as one that produces a powder X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings: 8.54, 4.27, 4.02 and 3.98 (Å), and a powder X-ray diffraction spectrum comprising reflections at 15.4, 31.1, 33.1 and 33.4 degrees 2θ.

(4) I have also reviewed and am familiar with Lafon, U.S. Patent No. 4,177,290 ("the Lafon '290 patent"). The Lafon '290 patent describes the preparation of

"benzhydrylsulphinylacetamide" which is an alternative chemical name for modafinil (also referred to as CRL 40476).

(5) The preparatory methods described in the Lafon '290 patent produce the modafinil racemate, not the individual (+/-) enantiomers of modafinil. Accordingly, the statement in the instant application that "l-modafinil and d-modafinil prepared according to the conditions described in US patent 4,177,290 are obtained in the form of one polymorphic form described as form I" is erroneous. The Lafon '290 patent does not teach or suggest the preparation of any specific forms of (-)-modafinil, let alone the Form I polymorph. Indeed, the Lafon '290 patent does not even indicate that racemic modafinil may exist in multiple polymorphic forms.

(6) I have also reviewed and am familiar with Lafon, U.S. Patent No. 4,927,855 ("the Lafon '855 patent"). Preparation I, at column 3, lines 5 to 57 of the Lafon '855 patent, describes the synthesis of (-)benzhydrylsulfinylacetamide, which is a chemical name for the compound known as (-)-modafinil (also referred to as CRL 40982, l-modafinil, or armodafinil). In the final step of the described synthesis, the residue is taken up in ether, the product filtered off and "recrystallized from ethanol to give CRL 40 982." At column 3, lines 53 to 55, the Lafon '855 patent indicates that the product of Preparation I is in the form of white crystals that are soluble in alcohols and acetone and insoluble in water and ether. The melting point (inst.) of the product is said to be 153° - 154°C.[1]

(7) The experiment underlying Preparation I of the Lafon '855 patent was performed at Laboratoire L. Lafon (now Cephalon France) a number of years ago. After research and investigation into their files, scientists and others at Cephalon France and Organisation De Synthese Mondaile Orsymonde have been unable to locate any remaining samples of this batch of (-)-modafinil, or any record of a powder X-Ray diffraction (PXRD) spectrum ever having been obtained on a sample of this batch. To the best of my knowledge, the product of the experiment that provides the basis of Preparation I has never been analyzed

[1] The abbreviation "inst." in the Lafon '855 patent indicates that the value given is an "instantaneous" melting point. Instantaneous melting points are obtained using a device such as a Kofler hot bar which has an electrically heated stage that is designed to have a nearly linear temperature gradient along its length. The instantaneous melting point is obtained by placing a thin layer of the sample on the hot stage along the temperature gradient, and identifying the point on the stage where melting occurs. Scientists at Cephalon France familiar with the experiment that underlies Preparation I in the '855 patent have advised that a Kofler hot bar was used to obtain the instantaneous melting point reported in Preparation I.

by PXRD or any other analytical method capable of identifying and/or distinguishing polymorphic forms of (-)-modafinil.

(8) The Lafon '855 patent nowhere teaches or suggests that (-)-modafinil may take on different polymorphic forms, or that the product of Preparation I is a polymorph, as opposed to some other crystalline form. Nor does the patent teach or suggest the specific Form I polymorph recited in the instant application. Moreover, the reference provides no information regarding the PXRD spectrum of the product. Thus, the Lafon '855 patent fails to provide any express disclosure of the Form I (-)-modafinil polymorph that is described and claimed in the present application.

(9) It is known in the art that different recrystallization conditions can have a significant impact on the solid form produced and minor variations in the conditions can lead to different polymorphic forms. The Lafon '855 patent is silent regarding the detailed conditions under which the ethanol recrystallization utilized in Preparation I was performed. The patent does not specify any particular grade of ethanol, and the concentration of the (-)-modafinil/ethanol solution used in the recrystallization is likewise not described. Moreover, no process conditions for the recrystallization are set forth. For example, the Lafon '855 patent does not indicate whether the solution was heated to dissolve the (-)-modafinil, and if so, whether it was heated to reflux. The patent also does not teach a rate at which the solution was then cooled, to what temperature, how the solvent was removed, or how the product was dried.

(10) I am aware that scientists at Cephalon France and Organisation De Synthese Mondaile Orsymonde, as part of their ongoing work with modafinil and its enantiomers, have on several occasions obtained PXRD spectra of polymorphic forms of (-)-modafinil that have been recrystallized from ethanol. Although this work was not performed under my direction and control, I have reviewed the data and reports and conferred with scientists involved with the experiments. The experimental conditions recorded by the scientists in their lab notebooks, and the polymorphic form[2] obtained from these recrystallizations, have been compiled and are set forth in the table attached hereto as Exhibit 2.

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[2] The terms Form I, Form II and Form IV used herein to designate different polymorphic forms of (-)-modafinil corresponds to the nomenclature set forth in the instant application.

(11) The recrystallizations set forth in Exhibit 2 generally entailed mixing (-)-modafinil with either absolute ethanol, denatured ethanol (*i.e.*, a mixture of 97.5% ethanol and 2.5% toluene), or either one of these grades of ethanol with 3% water added, heating to dissolve the (-)-modafinil, followed by cooling in an ice bath. The (-)-modafinil crystals were then collected by filtration, dried and analyzed sometime thereafter by PXRD.

(12) The data reported in Exhibit 2 shows that one of the recrystallizations yielded a mixture of Form I and Form IV,[3] one of the recrystallizations yielded Form II, and the remainder yielded Form I. A composite image showing the PXRD spectra obtained for Example Nos. ON II/149E,.ON II/149H, ON II/150A and ON II/150B is attached hereto as Exhibit 3. It is evident from this image that the X-ray diffraction spectrum for Example No. ON II/149H (second from bottom) is different than the X-ray diffraction spectrum of the other three examples.

(13) The experiments reported in Exhibit 2 show that a different polymorph was produced when using denatured ethanol as the solvent (Example No. ON II/149H) than when using absolute ethanol as the solvent (Example No. ON II/149E). Moreover, a comparison of Example No. ON II/149H and Example No. 1/0920 show that two recrystallizations from denatured ethanol do not always yield the same polymorphic form of (-)-modafinil.

(14) The experiments reported in Exhibit 2 also show that recrystallization from absolute ethanol in one instance (Example No. 5/2502) produced Form I (-)-modafinil, but in another instance (Example No. 1/0054a) produced a mixture of Form I and Form IV.[4]

(15) In view of these experiments, it is my opinion that recrystallization of (-)-modafinil from ethanol produces more than one form of (-)-modafinil, and does not necessarily produce Form I (-)-modafinil.

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[3] When a second PXRD was performed on a sample from this batch five years later, the sample was found to be only Form I (-)-modafinil.

[4] Experiments 1/0054(a) and 1/0054(b) also show that one polymorphic form of (-)-modafinil may spontaneously convert to a more stable polymorphic form over time. Specifically, when first examined about 9 months after the recrystallization was performed, this sample was found to produce an X-ray diffraction spectrum characteristic of a mixture of Form I and Form IV (-)-modafinil. However, when examined about 5 years later, the sample was found to produce an X-ray diffraction spectrum characteristic of pure Form I (-)-modafinil. I do not consider this finding to be unexpected or surprising;, as the Applicants have stated in the present application, that Form I is the more thermodynamically stable polymorphic form of (-)-modafinil.

(16) I have reviewed and am familiar with the data reported in the Declaration of Erwin Blomsma, Ph.D., prepared for submission in the instant application. Dr. Blomsma indicates that three distinct polymorphs of (-)-modafinil were obtained from ethanol recrystallization. The polymorphic form denominated Form A by Dr. Blomsma appears to correspond to the Form I (-)-modafinil polymorph of the instant application. I agree with Dr. Blomsma's conclusions, based on that data, that recrystallization of (-)-modafinil from ethanol under varying conditions can produce more than one crystalline form of the compound.

(17) I have reviewed and am familiar with the data reported in the Declaration of Matthew Peterson, Ph.D., also prepared for submission in the instant application. Dr. Peterson indicates that two distinct polymorphs of (-)-modafinil were obtained from ethanol recrystallization. The polymorphic form denominated Form E by Dr. Blomsma appears to correspond to the Form I (-)-modafinil polymorph of the instant application. I agree with Dr. Peterson's conclusions, based on that data, that different polymorphic forms of the compound may be produced depending upon the conditions under which ethanol recrystallization is performed.

(18) The data obtained by scientists at Cephalon France and Organisation De Synthese Mondaile Orsymonde, together with the data reported in the Declaration of Erwin Blomsma, Ph.D. and the Declaration of Matthew Peterson, Ph.D., show that varying the conditions under which (-)-modafinil is recrystallized from ethanol (such as the rate of cooling, the type of ethanol utilized, the (-)-modafinil concentration, the length of time the crystals are held at the final crystallization temperature prior to analysis, and other factors) produces different polymorphic forms. On the basis of this data, I conclude that without detailed information regarding such conditions, one cannot predict with any degree of certainty what polymorphic form will be produced by recrystallization of (-)-modafinil from ethanol.

(19) Scientists at Cephalon France and Organisation De Synthese Mondaile Orsymonde have measured the instantaneous melting point of known polymorphic forms of (-)-modafinil at various times over the course of several years. Instantaneous melting points were obtained using a Kofler hot bar, described previously, which, to my knowledge and understanding, is the same instrument used to obtain the melting point of the (-)-modafinil sample produced in Preparation I of the '855 patent. The table attached hereto as Exhibit 4

presents this instantaneous melting point data.[5] The data in this table shows that measurements of the instantaneous melting point of Form I (-)-modafinil ranged between 159° - 164°C, while the instantaneous melting point of Form II (-)-modafinil was found to be 156°C. Measurements of the instantaneous melting point of Form I mixed with another polymorph (either Form II or Form IV) of (-)-modafinil ranged between 156° - 164°C.

(20) The data reported in Exhibit 4 shows that the instantaneous melting point of Form I (-)-modafinil, as measured with a Kofler hot bar, ranges between 159° - 164°C. The product of Preparation I of the '855 patent is reported to have an instantaneous melting point (also obtained using a Kofler hot bar) of 153° - 154°C, which is outside this range, and closer to the instantaneous melting point obtained for Form II (-)-modafinil.[6] While, in my opinion, one cannot conclusively determine from this data which crystalline form was produced by Preparation I of the Lafon '855 patent, since the instantaneous melting point reported in the Lafon '855 patent does not appear to correspond to the instantaneous melting point of Form I (-) modafinil, the data supports a conclusion that the (-)-modafinil described in Preparation I of the Lafon '855 patent is NOT the claimed Form I (-)-modafinil.

(21) On the basis of the melting point experiments reported in paragraphs (19) and (20), it is my considered opinion that the product obtained by Preparation I of the Lafon '855 patent was not necessarily the claimed Form I (-)-modafinil polymorph. In my opinion one cannot, based on the teaching of an instantaneous melting point of 153° - 154°C, conclude

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[5] In the interest of full disclosure, it is noted that Exhibit 4 does not include Example No. 5/2173, which involved recrystallizing (-)-modafinil from isopropanol. The product of this example was found to have an instantaneous melting point of 153° - 154°C when first prepared, but its PXRD spectrum was not taken at that time, so it is not known what polymorphic form was present when the instantaneous melting point was identified. Three years later, the sample was analyzed by PXRD, and found to produce a spectrum consistent with Form I (-)-modafinil. However, no instantaneous melting point was taken at this time. Thus, there was never a contemporaneous assessment of both instantaneous melting point and PXRD for this sample. Since it is possible that the sample may have converted to Form I (-)-modafinil during storage (see footnote 4, above), this lack of contemporaneous correlation between instantaneous melting point and PXRD spectrum renders correlation of the data for this sample unreliable. Accordingly, data relating to Example No. 5/2173 was not included in Exhibit 4.

Similarly, Example No. 1/0054(b) (shown in Exhibit 2, and discussed previously) was not included in Exhibit 4, because the only instantaneous melting point obtained for the sample (164°C) was taken some five years prior to obtaining the corresponding PXRD spectrum (shown to be Form I). The melting point of 164°C obtained for Example No. 1/0054(a) is included in Exhibit 4, however, because the melting point was obtained within several months of obtaining the corresponding PXRD spectrum (shown to be a mixture of Form I and Form IV).

[6] If one were to include the two excluded samples referenced in footnote 5, the instantaneous melting point range for Form I (-)-modafinil would range between 153° - 164°C, and overlap with the instantaneous melting point obtained for Form II (-)-modafinil (156°C). As such, one would be unable to distinguish between polymorphic forms on the basis of instantaneous melting point.

that Preparation I of the Lafon '855 patent necessarily describes the claimed Form I (-)-modafinil polymorph.[7]

(22) As noted in paragraph (8) above, based on my review of the Lafon '855 patent, I conclude that the reference does not expressly describe Form I (-)-modafinil. Moreover, as noted above, one cannot conclude from the teaching in the Lafon '855 patent that the reported crystalline form of (-)-modafinil having an instantaneous melting point of 153° - 154°C is Form I (-)-modafinil.

(23) The data reported herein shows that recrystallization from ethanol may lead to Form I (-)-modafinil but also produces other polymorphic forms. The data further shows that varying the conditions under which ethanol recrystallization is performed, such as the rate of cooling, the grade of ethanol utilized, the (-)-modafinil concentration, and the length of time the crystals are held at the final crystallization temperature prior to analysis produces different polymorphic forms, and one cannot predict that a specific polymorphic form will necessarily be produced by recrystallization of (-)-modafinil from ethanol without information regarding such variables. Since the Lafon '855 patent does not provide information on these conditions, I conclude that Form I (-)-modafinil is not the natural or necessary result flowing from the teaching or practice of the Lafon '855 patent.

(24) I have read and am familiar with U.S. 2004/0102523 A1 ("the Broquaire, et al. application"). This application describes several polymorphic forms of the modafinil racemate, along with their PXRD spectra. The Broquaire et al. application does not describe any polymorphic forms of (-)-modafinil, and none of the polymorphs described in Broquaire et al. exhibit the PXRD spectrum of the Form I (-)-modafinil polymorph that is the subject of the present application.

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[7] In the interest of full disclosure, it is noted that I, and other scientists at Cephalon, Inc., have measured the melting point of samples of (-)-modafinil using means different from the Hofler hot bar device used to measure instantaneous melting points. These melting points were obtained on a different type of instrument, by a different method that involved progressively raising the temperature of a sample at a rate of 3-7°C/minute, and identifying the temperature range at which melting occurred. The results of these experiments are shown in Exhibit 5. The melting point obtained for samples of Form I (-)-modafinil ranged between 146.9 – 157 °C, while the melting point of Form II (-)-modafinil ranged between 146 – 149.6 °C. A mixture of Form I and Form II was found to have a melting point of 151.6 – 152 °C. These values are, in general, several degrees lower than the instantaneous melting points obtained with the Kofler hot bar. Accordingly, the absolute values obtained using different instrumentation cannot be directly compared. However, this data is internally consistent with Form I (-)-modafinil having a higher melting point range than other polymorphic forms of (-)-modafinil.

(25) I have also read and am familiar with WO 02/10125 ("the Singer, et al. reference"). This reference describes polymorphic forms of modafinil, but provides no disclosure of polymorphic forms of (-)-modafinil. Moreover none of the polymorphs described in Singer et al. produce a PXRD spectrum that corresponds to the PXRD spectrum of the Form I (-)-modafinil polymorph that is claimed in the present invention.

(26) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June 7, 2006

John P. Mallamo

John P. Mallamo, Ph.D.

EXHIBIT 1

John P. Mallamo, Ph.D.

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Work Address:
Cephalon, Inc.
145 BrandywinePkwy.
West Chester,PA 19380
(610)-738-6366

Education:

B.S. Chemistry, Colorado State University, Fort Collins, CO, 1977
Undergraduate Research Fellowships in Chemistry 1974-1977 (in the labs of A.I. Meyers and K.E. DeBruin)

Ph.D. Organic Chemistry, Johns Hopkins University, Baltimore, MD, 1981 (Biochemistry as Second)
E.M. Marks Award in Organic Chemistry, 1980
Thesis Advisor: Professor Gary H. Posner

Thesis Title: Part 1 - Sequential Carbon -Carbon Bond Formation: Cascade Annulations.
Part 2 - Asymmetric Induction during Conjugate Addition to Chiral a,b-Ethylenic Sulfoxides

Employment Positions Accepted:

September 1981, Sterling-Winthrop Research Institute
Medicinal Chemistry Department, Senior Research Chemist

January 1994, Cephalon Inc.
Director of Chemistry

Job Titles:

Sterling Drug, Inc. 9/81 – 12/93 (Sanofi-Winthrop)

1982 Assoc Project Chemist (Mentorship program) – Cardiovascular.
1983 Project Chemist - Antiviral Program (Discovered Phase 1 compound WIN54954)
1985 Group Leader, Medicinal Chemistry. Antivirals and Steroid receptor ligand projects.
1986 Project Chemist - Prostatic Diseases Program (Discovered Zanoterone®, 2 backups in development)
1987 Group Leader II - (Designed Danazol SBA – prodrug of existing product)
1989 Project Chemist - Neurodegeneration, Excitatory Amino Acid Antagonists.
1990 Principal Investigator
1991 Assistant Research Director, Medicinal Chemistry and Discovery KiloLab
1992 Therapeutic Area Co-Chair, Director Neuroscience Research (Discovered development candidate compound WIN63480)

Cephalon, Inc. 1/94 - present

1994 Director, Chemical Research - Cephalon, Inc.
1995 Senior Director, Medicinal Chemistry
1998 Vice President, Drug Discovery
1999 Vice President, Drug Discovery and Chemical Development
2002 Vice President, WW Chemical R&D

Current Responsibilities:
Lead a team of department directors with a mission to design and direct the synthesis, and evaluation of compounds with novel structure/activity - ensure the timely emergence and aggressive development of new chemical leads. Direct/lead the research and activities of the Departments of Medicinal Chemistry, Hit-to-Lead, Computational Chemistry and Chemical Development resulting in a regular/timely schedule of IND and NDA filings. Organizational responsibility for more than 65 chemists and engineers.

Coordinate worldwide activities in all aspects of organic chemistry as applied to the pharmaceutical industry. Coordinate all chemical process research activities providing efficient syntheses of key molecules. Ensure the timely synthesis of cGMP grade samples for development and clinical purposes through Phase 2. Leadership and line-management responsibilities for pilot plant operations in the US and France. Ensure appropriate process engineering enabling event-free Manufacturing Development. Interface with and serve on senior management teams several corporate collaborations and joint ventures. Ensure compliance with budgetary allocations.

Related Experience:

Antihypertensives (PDE inhibitors).
Antirheumatics, Antiinflammatories.
Antivirals (Picornavirus, Rhinovirus).
Antiandrogens (Prostatic Diseases).
Opiate and Non-Opiate Analgesics.
Antipsychotics (atypical).
Excitatory Amino Acid Antagonists.
Neurotrophic Molecules.
b-Amyloid Processing.
Antiproliferatives (Oncology).
Kinase Inhibitors.
Protease inhibitors.
Patent Law.
Computational Chemistry/Molecular Modeling.
Combinatorial Chemistry/Parallel Synthesis/Automated Chemistry

Special Training:

Performance Management, September 1992.
Managing Conflict, January 1992.
Key Manager Training, 1990-1992.
Completed Staffwork Workshop, January 1990.
Managing a Diverse Workforce, October 1989.
Frontline Leadership Program, 1988-1990 (a Kodak sponsored 3 year program).
Effective Presentations, March 1986.
Conducting Performance Appraisals, 1983, 1986, 1990, 1994, 1998.
Chemical Design Ltd.-Chemx Introductory and Advanced Courses.
Tripos Assoc. - Sybyl Intermediate and Advanced Courses, SPL Programming, Sybyl QSAR, ComFA.

Oral Presentations/Abstracts

R. Tripathy, J. Singh, E.R. Bacon, T.S Angeles, S.X. Yang, M.S. Albom, L. Aimone, J. Herman, C. Robinson, H. Chang, B.A. Ruggeri, C. Dionne, J. P. Mallamo, "1,2,3 Thiadiazole substituted Pyrazolones: Potent VEGFR2/KDR Kinase inhibitors." Presented at the 226th National ACS Meeting, NY, NY, September 7-11, 2003.

R. Tripathy, A. Reiboldt, P.A. Messina, G. Hostetler, R.M. Giuliano, > Iqbal, J. Singh, E. R. Bacon, T.S. Angeles, S.X. Yang, M.S. Albom, L. Aimone, C. Robinson, H. Chang, B.A. Ruggeri, C. Dionne, and J.P. Mallamo, Heterocyclic Substituted Pyrazolones. A potent class of VEGFR-2 kinase inhibitors. Presented at the 28th National Medicinal Chemistry Symposium, June 2002.

D. Gingrich, R. Hudkins, D. Reddy, J. Singh, B. Ruggeri, C. Robinson, H. Chang, K. Hunter, C. Dionne, and J. Mallamo Identification, SAR and Preclinical Development of a Novel Inhibitor of VEGF-dependent Angiogenisis. CEP-7055. Presented at the 223rd National ACS Meeting, Orlando Florida, April 2002. First Disclosure conference. Cited in C&E News

T. Underiner, M. Iqbal, J. Mallamo, D. Reddy, A. Reiboldt, J. Singh, and R. Tripathy, "C12, N13 Heterocyclic Bridiged Fused Pyrroloindenocarbazoles. Paper #622, 222nd ACS National Meeting, August 26-30, 2001.

J. Mallamo "New Inhibitors of rh-Calpain I", Presented at the First ITB Conference, Montreal, CN, April 18, 1999.

R. Hudkins, C. Murakata, M. Kaneko. T. Angeles, C. Dionne, N. Neff, J. Vaught, and J. Mallamo "Selective trk-A tyrosine kinase inhibitors", Presented at the 214th ACS Meeting, Dallas, Texas, April 1998.

G.J. Wells, R. Tripathy, J.P. Mallamo, R. Bihovsky, M.A. Ator, S. Mallya, S.E. Senadhi, D. Bozycko-Coyne, and R. Siman, "Dipeptidyl Benzotriazol-1-yl- and Benzotriazin-4-one-3-yl oxomethyl ketones as potent, highly selective inhibitors of Calpain I", presented at the 213th ACS Meeting Las Vegas, Nevada, September 1997.

J.P. Mallamo, et. al., "Neurotrophic Derivatives of K252a." presented at the 50th Anniversary Gordon Research Conference on Medicinal Chemistry. Colby-Sawyer College, NH, August 3-7, 1997.

Jani, J.P., Emerson, E., Camoratto, A.M., Hudkins, R.L., Mallamo, J.P., Murakata, C., Issacs, J., Skell, J., Neff, N., Vaught, J., and Dionne, C., "Evaluation of the antitumor efficacy of CEP-2563 for the treatment of prostate cancer." Proceedings of the American Association for Cancer Research (AACR) 88:3148 (1997)

J.P. Mallamo, "Novel and Selective Inhibitors of Calpain: Unexpected P2 Tolerance." Presented at the International Symposium on the Calpains: Role in Neurodegeneration, Oxford University, UK, April 12, 1997.

J.P. Mallamo, et. al., "Potent and Selective Neurotrophic Derivatives of K252a. SAR of Survival Promoting Analogs." Presented at the 211th National ACS Meeting, Orlando FL., August 23, 1996.

J.P. Mallamo, J.C. Kauer, R.L. Hudkins, D.P. Rotella, M.A. Glicksman, M. Saporito, S. Carswell, F. Haun, E. Knight Jr., N.T. Neff, J.L. Vaught, C. Murakata, M. Kaneko, "Potent and Selective Neurotrophic Derivatives of K252a." Presented at the Western Biotechnology Conference, San Diego CA, October 19, 1995.

J.P. Mallamo, J.C. Kauer, R.L. Hudkins, D.P. Rotella, M.A. Glicksman, M. Saporito, S. Carswell, F. Haun, E. Knight Jr., N.T. Neff, J.L. Vaught, C. Murakata, M. Kaneko, "Potent and Selective Neurotrophic Derivatives of K252a. Presented at the Second Symposium on Medicinal Chemistry Approaches to Alzheimer's Disease, Strasbourg, France, August 28, 1995.

R.L. Hudkins, J.P. Mallamo, J.C. Kauer, M.A. Glicksman, E. Knight Jr., N.T. Neff, J.L. Vaught, C. Murakata, M. Kaneko, "Structure-Activity Relationships of Neurotrophic Derivatives of K252a. Presented at the Second Symposium on Medicinal Chemistry Approaches to Alzheimer's Disease, Strasbourg, France, August 28, 1995.

M. Reuman, J.P. Mallamo, D.L. DeHaven-Hudkins, "Synthesis and Binding Affinity of 2,3,3a,4,9,9a-Hexahydro-9,4-(iminomethano)-1H-benz[f]indenes. Ligands for the PCP site of the NMDA Receptor." Presented at the Winter Conference on Medicinal and Bioorganic Chemistry, Steamboat Springs, CO., January 1995.

B. Ault, D. Luttinger, S.J. Ward, J.P. Mallamo, D. Martin, T.E. Salt, S.A. Eaton, X. Zheng, R.S. Zukin, M.S. Miller, "WIN 63480, A High Affinity Uncompetitive NMDA Channel Blocker, has Reduced Closed Channel Access Compared to MK-801" Presented at the Society for Neuroscience Meeting, Miami Beach, Florida, November 13-18, 1994.

Miller, M.S., Ault, B., DeHaven-Hudkins, D.L., Earley, W.G., Luttinger, D., Mallamo, J.P., and Ward, S.J. "WIN 63480: A Novel, Open Channel-Selective NMDA-Antagonist with Antiischemic Activity." Presented at the Society for Neuroscience Meeting, Miami Beach, Florida, November 13-18, 1994.

D.L. DeHaven-Hudkins, F.Y. Ford-Rice, J.D. Daubert, W. Earley, J.P. Mallamo, L.F. Lanyon, " Binding of the Novel Ligand [3H] WIN 63480 to the Phencyclidine (PCP) Receptor." Presented at The Society for Neuroscience Meeting, November 13-18, 1994.

T.R. Bailey, G.D. Diana, J.P. Mallamo, D. Cutcliffe, P.M. Carabateas, N. Vescio, R.C. Ogelsby, D.C. Pevear, "A Comparison of Antipicornaviral Activity between Selected 2-Acetylfurans and their Isoxazole Counterparts: Are 2-Acetylfurans Bioisosteres for 3-Methylisoxazoles?" presented at the National ACS Meeting, August, 1993.

Michael Reuman, J. Wetzel, and J.P. Mallamo, "On the Addition of Benzonitrileoxide to 1,1,1-Trifluoropropyne." presented at the Gordon Research Conference - Reactions & Procedures. 1993.

Guy D. Diana, D.M. Volkots, D. Cutcliffe, R.C. Ogelsby, T.R. Bailey, J.P. Mallamo, T.J. Nitz and D.C. Pevear, "The Evaluation of Tetrazole Analogues Related to WIN 54954 Against Picornaviruses" Presented at the Wellcome Symposium in Antiviral Therapy, December 6, 1992.

John P. Mallamo, and J.R. Wetzel, "Synthesis of the 6-Oxo, 8,9,10-trifluoro-1H-pyrimido[1,2-c]quinoline and the 6-Oxo, 8,9,10-trifluoro-6H-benzo[c]quinoline Ring Systems" Presented at the 204th ACS National Meeting, Washington, D.C., August 23-28, 1992.

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Patents and Applications: (Foreign equivalents/applications of U.S. Patents not listed)

U.S. Patent # 5,053,405 :	Antiandrogenic Sulfonlysteroidothiazoles.
U.S. Patent # 5,068,234 :	3-arylcarbonly-1-(C-attached-N-ereroaryl)-1H-Indoles
U.S. Patent # 5,134,135 :	Antiandrogenic Sulfonylsteroidooxazoles.
U.S. Patent # 5,239,110 :	Phenylcyclohexanol derivatives as agents for treating CNS disorders.
U.S. Patent # 5,240,935 :	Substituted 2-azabicyclo[2.2.2]octane derivatives and compositions and method of use thereof
U.S. Patent # 5,286,733 :	Substituted 3-piperidinealkanoates and alkanones and compositions and method of use thereof
U.S. Patent # 5,290,789 :	Penta and tetrasubstituted piperidines and compositions and method of treating psychosis
U.S. Patent # 5,290,796 :	Substituted 3-piperidinealkanamines and alkanamides and compositions and method of use thereof
U.S. Patent # 5,324,737 :	3-Arylcarbonyl-1-(C-attached-N-heteryl)-1H-Indoles.
U.S. Patent # 5,364,867 :	4-phenylpiperdine agents for treating CNS disorders
U.S. Patent # 5,380,729 :	12-Hetero Substituted 6,11-Ethano-6,11-Dihydrobenzo[b]quinolizinium Salts and Compositions and Method of use thereof.
U.S. Patent # 5,430,036 :	6,11-substituted-6,11-dihydrobenzo[b]quinolizinium salts and compositions and method of use thereof.
U.S. Patent # 5,434,159 :	6,11-cyclyl-1,2,3,4,5,6,11,11a-octahydrobenzo[b]quinolines and compositions and method of use thereof.
U.S. Patent # 5,455,248 :	Substituted 6,11-Ethano-6,11-Dihydrobenzo[b]quinolizinium Salts and Compositions and Method of use thereof.
U.S. Patent # 5,498,616 :	Cysteine Protease and Serine Protease Inhibitors.
U.S. Patent # 5,554,620 :	Substituted 6,11-ethano-6,11-dihydrobenzo[b]quinolizinium salts and compositions and methods of use thereof.
U.S. Patent # 5,569,655 :	Substituted Heterocyclylisoquinolinium Salts and Compositions and Methods of use Thereof.
U.S. Patent # 5,604,224 :	Substituted heterocyclylisoquinolinium salts and compositions and methods of use thereof.
U.S. Patent # 5,631,264 :	Substituted 6,11-Ethano-6,11-dihydrobenzo[b]quinolizinium salts and compositions and methods of use thereof.
U.S. Patent # 5,639,732 :	Phosphorous-Containing Cysteine and Serine Protease Inhibitors.
U.S. Patent # 5,650,407 :	Selected Soluble Esters of Hydroxyl-Containing Indolocarbazoles.
U.S. Patent # 5,658,906 :	Cysteine and Serine Protease Inhibitors.
U.S. Patent # 5,686,444 :	Selected Soluble Esters of Hydroxyl-Containing Indolocarbazoles.
U.S. Patent # 5,736,696 :	Selected Derivatives of K252a.
U.S. Patent # 5,817,651 :	3-Arylcarbonyl-1-(C-Attached-N-Hereryl-1H-Indoles.
U.S. Patent # 6,083,944 :	Quinoline-containing alpha ketoamide cysteine and serine protease inhibitors.
U.S. Patent # 6,096,778 :	Alpha ketoamide multicatalytic protease inhibitors.
U.S. Patent # 6,100,267 :	Quinoline and naphthalenecarboxamides, pharmaceutical compositions and methods of inhibiting calpain.
U.S. Patent # 6,127,401 :	Bridged indenopyrrolocarbazoles.
U.S. Patent # 6,150,378 :	Peptidyl-containing alpha-ketoamide cysteine and serine protease inhibitors.
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U.S. Patent # 6,310,057 :	alpha-ketoamide Multicatalytic Protease Inhibitors.
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U.S. Patent # 6,492,396 :	Substituted thioacetamides.
U.S. Patent # 6,670,358 :	Substituted thioacetamides
U.S. Patent # 6,686,335 :	Hydroxamate-containing cysteine and Serine Protease inhibitors.
U.S. Patent # 6,703,368 :	Peptide-containing a-ketoamide Cysteine and Serine Protease Inhibitors.
U.S. Patent # 6,875,865 :	Selected derivatives of K252a.
U.S. Patent # 6,919,367 :	Substituted thioacetamides.

Computer Literacy:
SYBYL, AMPAC/MOPAC, Gaussian Series, MDL Software (MACCS, REACCS, ISIS), VAX-VMS, Oracle-SQL, Macintosh OS, MS-DOS, Windows, some UNIX and vBASIC. Advanced understanding of computational sciences as applied to drug discovery and development.

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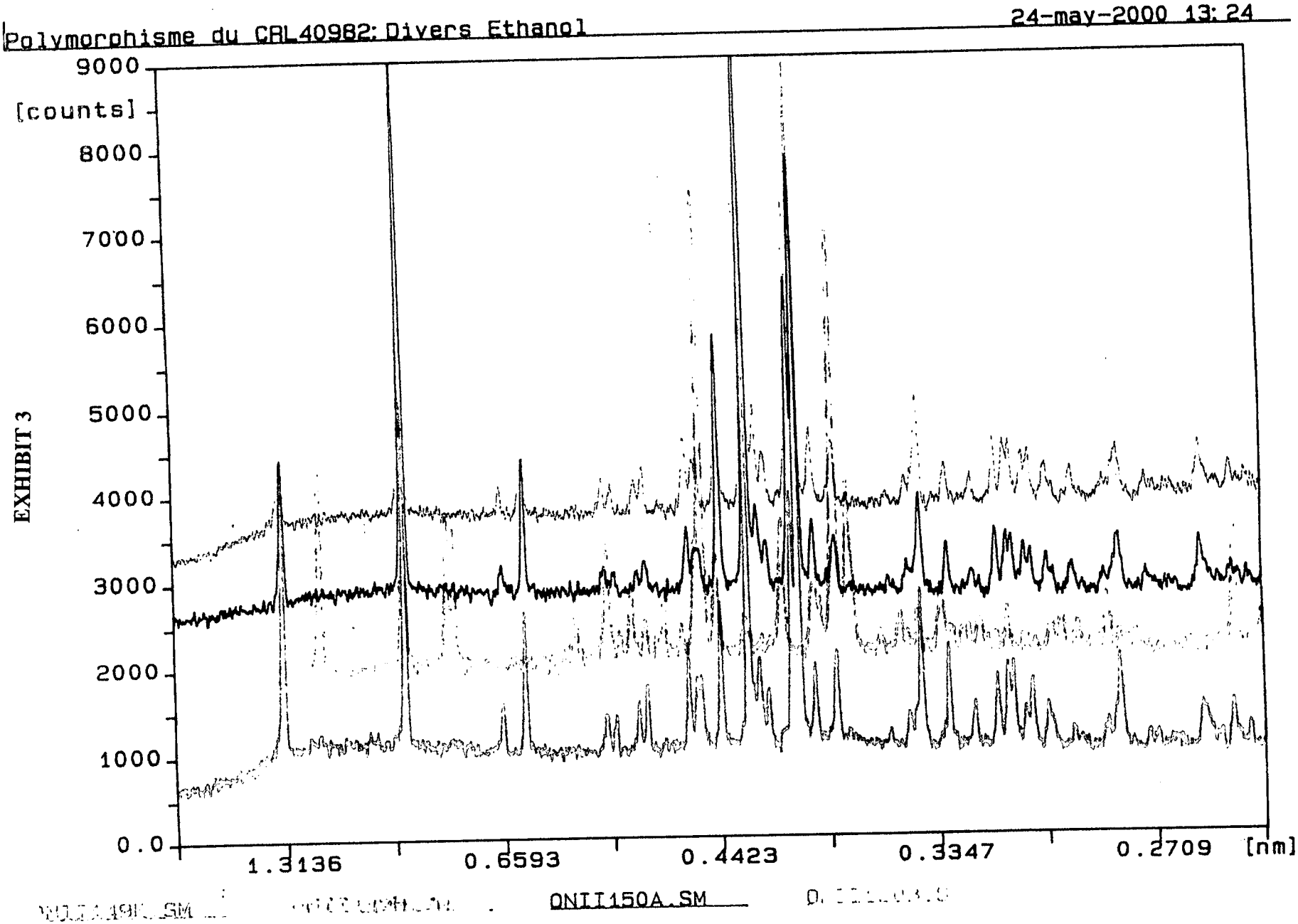
Editorial Board, IDdb Patent Alerts - Neuroscience (1995- present). Current Drugs.
Science Advisory Board, IDdb Publications 1995 – present
Session Chair and Organizer, 1997 Gordon Research Conference (Med. Chem.) - Neurotrophic Molecules.
Session Chair and Organizer 2000 Gordon Research Conference (Med. Chem) -- Poster Session
Session Chair and Organizer, 3rd Med Chem. Conference on Neurodegenerative Diseases. 1998
Conference Organizer, 4th International Med. Chem Conference on Neurodegenerative Diseases (February 2000).
Poster Session Chairperson – 2001 Medicinal Chemistry Gordon Conference
Board of Directors, Medicinal Chemistry of Neurodegenerative Diseases Foundation 1996-present
Board of Technical Directors, Nanotechnology Institute – Ben Franklin Technology partners
Nominated to Board of Directors, Synexis, Inc. (declined due to conflict of interest). 2002

EXHIBIT 2

Example No.	Recrystallization Procedure	Form Obtained
5/2502	(-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 100 g of the crude product was taken up in 500 ml absolute EtOH, heated to reflux, filtered, allowed to come to room temperature, then cooled in an ice bath. Crystals were filtered and dried. Yield 77 g. M.P. (inst.)= 153-154°C. These crystals were then dissolved in 500 ml absolute ethanol, heated to reflux, then left to cool to room temperature, with stirring. The crystals were filtered and dried. M.P. (inst.)= 163-164°C. PXRD analysis performed about 1 month later with a PW1840(Cu) diffractometer.	Form I
1/0054(a)	Crystals of (-)-modafinil were obtained by the same double recrystallization procedure set forth for Example 5/2502, on a larger scale. 163.5 g of product was obtained. M.P. (inst.)= 164°C. PXRD analysis performed about 9 months later with a PW1840(Cu) diffractometer.	Form I/ Form IV mixture
1/0054(b)	Sample of Example No. 1/0054(a) (*supra*) taken from storage re-analyzed by PXRD 5 years later with a PW1840(Cr) diffractometer.	Form I
1/0920	(-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 365.8 g of crude product was taken up in 1.83 L of denatured EtOH (w/2.5% toluene) and heated to 75°C to dissolve, then allowed to crystallize. 162 g of these crystals were taken up in 810 ml denatured EtOH (w/2.5% toluene), and heated to reflux. Solution was allowed to cool on bench top for 10 minutes, then transferred to an ice bath. Crystals were filtered and dried under vacuum at 30°C. M.P. (inst.)= 163°C PXRD analysis performed 10 days later with a PW1840(Cr) diffractometer.	Form I

ON II/149 E	Step a: (-)-modafinil was synthesized by ammonolysis of methyl (-) benzhydrylsulfinylacetate in MeOH and water. 66 g of crude product was taken up in 330 ml absolute EtOH, heated to reflux, filtered, and the hot filtrate immediately cooled in an ice bath. Crystals were filtered and dried under vacuum at 35°C. Yield 57 g. Step b: 7.85 g of product from Step a was mixed with 115 ml absolute EtOH and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. M.P. (inst.)= 162°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form I
ON II/149 H	5 g of product from II/149 E Step a, was mixed with 80 ml denatured EtOH (w/2.5% toluene) and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. M.P. (inst.)= 156°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form II
ON II/150 A	Step a: product from II/149 E Step a, was dissolved in a mixture of acetone, ethyl acetate, methanol, isopropanol, absolute ethanol, and propanol. The solvents were evaporated under vacuum using a rotator. The residue was dissolved in absolute ethanol, cooled to 20 °C, then placed in an ice bath. Crystals were filtered and dried in an oven. Step b: About 5 g of the product from II/150 A, Step a, was mixed with 70 ml denatured EtOH(w/2.5% toluene) + 3% H_2O and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form I
ON II/150 B	About 5 g of the product from II/150 A, Step a, was mixed with 70 ml absolute EtOH + 3% H_2O and heated to reflux. The hot solution was placed in an ice bath for 30 minutes. Crystals were filtered and dried under vacuum at 35°C. PXRD analysis with a PW1840(Cr) diffractometer.	Form I


Polymorphisme du CRL40982: Divers Ethanol
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0.6593
0.4423
0.3347
0.2709
[nm]
ONII150A.SM

EXHIBIT 3

Exhibit 4

Polymorphic Form Tested	Instantaneous Melting Point (°C)
Form I	163-164
Form I/Form IV mixture	164
Form I	163
Form I/Form IV mixture	161
Form I/Form II mixture	160
Form I	159
Form I/Form II mixture	156
Form I	162
Form I/Form II mixture	156
Form I	162
Form II	156
Form I	160

Exhibit 5

Polymorphic Form Tested (Blind)	Non-instantaneous Melting Point (°C)
Form I	154-156.2
Form I	155-156
Form I	156-157
Form I	153.7-154.9
Form I	149.7-150.6
Form I/Form II mixture	151.6-152
Form II	146-147.2
Form II	146.5-149.6
Form I	146.9-148.1